

REMARKS

This Amendment responds to the July 8, 2004 Office Action in the above-referenced patent application.

1 Status of Claims

The status of the claims is summarized as follows:

Claims	Status
1-53	Pending
54-247	Withdrawn
248-281	Pending
282-370	Withdrawn
371-398	Pending
399-445	Withdrawn
446-458	Cancelled
459-467	Withdrawn

2 Interview Summary

The applicants appreciate the courtesy extended by the Examiner and the Examiner's supervisor in the July 28, 2004 interview (the "*Interview*"). The Examiner agreed to allow pending method claims 1-53, 248-281 and 371-398, and the applicants agreed to cancel compositions claims 446-458 so that these claims may be pursued in a separate application.

The arguments made by the applicants' representative in the Interview are summarized as follows: The applicants have been engaged for over ten years in the business of conjugating polymers to polypeptides in order to modify the pharmacokinetic properties of the polypeptides. One of the primary attributes of the polymers used by the applicants is that they inhibit enzymatic and chemical cleavage of the polypeptides. The applicants have now surprisingly discovered that insulin conjugates can be made using an approach in which a peptide is conjugated then cleaved to yield a conjugated product. For ease of reference, this approach is referred to by the applicants as a "conjugate-then-cleave" approach. The conjugate-then-cleave approach is not taught or suggested by the cited reference (Ekwuribe et al., U.S. Patent No. 6,309,633). Further, the applicants have surprisingly discovered that there are unsuspected advantages in the manufacturing of conjugated insulin molecules using the conjugate-then-cleave approach, such as prevention of over-cleavage, avoiding conjugation at the N-terminus, and/or modifying

solubility characteristics of the pro-product during the manufacturing process to facilitate isolation and/or purification.

3 Conclusion

Based on the arguments made during the Interview, as summarized above, and the arguments previously presented in the response to the January 16, 2004 Office Action, the applicants submit that the pending claims 1-53, 248-281 and 371-398 are now in condition for allowance.

No fee is believed to be due at this time; however, the U.S. Patent Office is authorized to pay any fee or charge properly payable in connection with the entry of this Amendment to Deposit Account No. 13-4365.


If any further issues remain to be addressed prior to issuance of a Notice of Allowance, the Examiner is requested to contact the undersigned attorney at (919) 286-8128.

Respectfully submitted,

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(Applicants)

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